

## **REMARKS**

The Examiner's Office Action mailed September 30, 2010, which rejected all pending claims, has been reviewed. Reconsideration in view of the foregoing amendments and remarks is respectfully requested. Moreover, Applicants have reviewed the Office Action of September 30, 2010, and submit that the above Amendments and the following Remarks are responsive to all points raised therein. Applicants believe that currently pending claims 1 and 4-5 are now in form for allowance.

### Status of Claims

Claims 1 and 4-5 are pending in the application. Claim 1 has been amended for further clarification. No new matter has been added.

### Rejection of Claims 1, and 4-5 under 35 USC 112, second paragraph

Reconsideration is requested of the rejection of claims 1, and 4-5 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have amended claim 1 and submit that the amendment is sufficient to overcome the rejection to claim 1. Applicants request the withdrawal of the rejection to claim 1.

### Rejection of Claims 1, and 4-5 under 35 USC 103(a)

Reconsideration is requested of the rejection of claims 1, and 3-7 under §103(a) as being unpatentable over Schulz et al (US 2003/0045544) in view of Vetter et al. (US 5808076) and Himmler et al (Abstracts of the interscience conference on Antimicrobial Agents and Chemotherapy (2002)).

The Examiner states that it would have been prima facie obvious for one skilled in the art at the time of the invention to use pradofloxacin to systemically treat bacterial infections of the oral cavity in humans or animals in need thereof. The Examiner states that "Shultz et al teaches the use of fluoroquinolones such

as pradofloxacin in topical and local treatment of oral cavity infections, Vetter teaches the systemic activity of fluoroquinolones against a broad spectrum of bacteria which includes species of oral cavity bacteria....Himmeler provides additional motivation to an ordinary skilled artisan to utilize pradofloxacin as it showed the lowest MIC ... in comparison to other fluoroquinolones in inhibiting *E.coli*, *S. aureus* and *S. intermedius*." (See Office action at page 11).

Applicants once again respectfully disagree with the Examiner. Applicants submit the expert report of Dr. Peter Fahrenkrug as a declaration to the present application. The expert report is submitted because it includes a detailed description of periodontal disease, the bacteria that cause it, the systemic implications, study data and interpretation of all of this information from a true expert's point of view.

In summary, Dr. Fahrenkrug states that periodontal disease is not caused by one or a few defined bacterial species, but is a complex polymicrobial infection that interacts with complex host defense mechanisms. It is characterized by a change from healthy periodontal flora mainly composed of Gram-positive non-motile cocci to the flora of periodontal disease dominated by aggressive anaerobic Gram-negative motile rods. *Porphyromonas* spp., *Prevotella* spp. and spirochetes are likely to be implicated in periodontal disease of dogs. Periodontal disease can have systemic consequences such as cardiovascular disease, endocarditis, pneumonia, stroke, as well as renal and hepatic disorders, all mediated via bacteraemia of LPS and cytokines being released into the bloodstream. There is no curative treatment of periodontal disease. However progression of the disease can be prevented by suitable periodontal treatment. Broad-spectrum antimicrobials are an important part of periodontal therapy. (See entire report and conclusions on page 29-30)

Dr. Fahrenkrug notes that only four products are currently registered for the use in oral infections and/or periodontal disease. These are 1) combination of metronidazole and spiramycin, 2) clindamycin hydrochloride, 3) amoxicillin/clavulanic acid, and 4) Doxycycline hyclate. The combination of metronidazole and spiramycin has a weakness against gram-negative aerobes.

Clindamycin does not extend to gram-negative aerobes. Amoxycillin/clavulanic acid shows more activity to gram-positive bacteria than gram-negative. Doxycycline has broad-spectrum against many gram-positive and gram-negative aerobes, however it has been taken from the market by the producer. Dr. Fahrenkrug also notes that none of the quinolones has been registered for the treatment of periodontal disease because of the lack of activity against anaerobic bacteria. Pradofloxacin, however, shows three fold increased activity against anaerobic bacteria than other veterinary quinolones (the study is also submitted with this response for the Examiner's review). Dr. Fahrenkrug also states that as there are only three products available and as increasing resistance rates to older products may be encountered, alternative products would be most welcome. (see pg 19 and 20 of the report).

The expert report also reviews 3 studies – 2 comparing pradofloxacin to metronidazole + spiramycin) and 1 comparing pradofloxacin to clindamycin hydrochloride, both established products in the treatment of periodontal disease (tabulated methodology and reports are also submitted with this response for the Examiner's review). Dr. Fahrenkrug finds that pradofloxacin exerted beneficial effects on the important clinical periodontal parameters pocket depth, loss of attachment and bleeding on probing in the studies. He also states that general clinical signs were alleviated, pradofloxacin was able to re-establish and stabilize healthy periodontal flora over prolonged periods of time and to reduce the total subgingival anaerobic count. (see pg. 30 of the report).

Applicants also submit a response sent by Applicants to the authorities showing the reason that we treat systemically is to attain high concentrations of pradofloxacin in the gingival tissue.

The Examiner states that Schultz teaches the use of fluoroquinolones, such as pradofloxacin in topical and local treatment of oral cavity infections and that Vetter teach the systemic activity of fluoroquinolones against a very broad spectrum of bacteria. The Examiner then states that an ordinary artisan would be motivated to combine the teachings of Schulz and Vetter to develop a method of treating bacterial infections of the oral cavity by systemic administration of

pradofloxacin and other fluoroquinolones. Applicants submit that an ordinary artisan would not have been motivated by Schultz and Vetter to develop this method because as stated by Dr. Fahrenkrug other fluoroquinolones were known to have unsatisfactory activity against periodontal disease (Vetter) and someone skilled in the art would only have tested pradofloxacin (taught in Schulz) systemically by using hindsight. The addition of Himmeler is not sufficient as Himmeler shows MIC of pradofloxacin compared to other fluoroquinolones against E.coli and two gram-positive anaerobes. As stated by Dr. Fahrenkrug an active ingredient has to show activity against a broad range of both gram-positive and gram-negative anaerobes, most importantly the gram-negative anaerobes. Himmeler does not provide such data. One gram-negative anaerobe does not lead someone skilled in the art to believe all gram-negative anaerobes would be equally affected.

In addition, now applicants have submitted on animal data comparing pradofloxacin against the registered products for treatment of periodontal disease and an expert's opinion stating that there is a need to be solved by the present invention that hasn't been solved by the existing or remaining products on the market.

Applicants submit that all of the above arguments, data, and Dr. Fahrenkrug's report taken together show that claims 1, 4, and 5 are patentable over Schultz et al. in view of Vetter et al. and Himmeler et al.

Conclusion

In view of the above, Applicants respectfully submit that the pending claims are novel and not obvious over the cited references and request withdrawal of all rejections and allowance of the claims.

The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment in connection with this amendment to Deposit Account No. 50-4260.

Respectfully submitted,

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